T113
+Y12
5635

MIGRAINE AND PSYCHOPATHOLOGY: AN ANALYSIS BY MIGRAINE SUBTYPE

GERALDINE TERESA MOSAVERO

1988

YALE

MEDICAL LIBRARY

Digitized by the Internet Archive
in 2017 with funding from
Arcadia Fund

https://archive.org/details/migrainepsychopa00moga

YALE MEDICAL LIBRARY
SEP 2 1988

Migraine and Psychopathology:
An Analysis by Migraine Subtype

A Thesis Submitted to the Yale University
School of Medicine in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Medicine

by
Geraldine Teresa Mogavero
1988

ABSTRACT

Migraine and Psychopathology:

An Analysis by Migraine Subtype

Geraldine Teresa Mogavero

1988

This study investigates the relationship between migraine and psychopathology in a sample of subjects in treatment for migraine. Several domains of psychopathology were assessed including psychiatric diagnoses, personality, temperament and social functioning. Seventy-one migraine patients were interviewed using a standardized diagnostic interview, the Schedule for Affective Disorders and Schizophrenia, and the Migraine Symptom Review. The lifetime prevalence of depression among subjects with migraine was 60%. Rates of anxiety disorders, notably panic disorder and phobic conditions, were also highly elevated. However, there was no difference in lifetime prevalence of psychopathology between various subtypes of migraine including the "classic" vs. "common" distinction or "menstrual migraine." "Menstrual migraine," though, was associated with less severe headaches and greater family history of migraine.

TABLE OF CONTENTS

Introduction.....1

Clinical Description and Classification.....4

Delimitation from Other Disorders.....5

Epidemiology.....7

Pathophysiology and Laboratory Study.....10

Treatment.....16

The "Migraine Personality" and Psychopathology.....19

"Menstrual Migraine".....22

Late Luteal Phase Dysphoric Disorder.....24

Proposal.....27

Materials and Methods.....29

Results.....31

Discussion.....42

Conclusion.....47

Appendix A.....50

Appendix B.....54

Bibliography.....60

> They seemed to be selfish, these headaches, and yet they were not. The pain was real. No one could simulate such agonizing pain. Mr. Pritchard dreaded them more than anything in the world. A good one could make the whole house vibrate with horror.(1)

Migraine headaches were initially described by Aretaeus of Capadocia during the 1st century A.D.(2) Despite the vast amount of medical knowledge accrued during the intervening centuries, migraine headaches remain an enigma to both neurologist and psychiatrist.

Current definitions of migraine headaches are based on proposals by the Ad Hoc Committee on the Classification of Headache in 1962. This committee, formed by the National Institute of Neurological Diseases and Blindness, divided the broad term "headache" into fifteen varieties.(3) "Vascular headaches of the migraine type" were recurring headaches, often unilateral and accompanied by anorexia, nausea and vomiting. They ranged in severity, duration and frequency, and were sometimes preceded by sensory, motor and mood alterations. Migraines were also noted to have a familial preponderance.(4)

"Muscle-Contraction headache," the second major class of headaches, was typified by a constricting pain or pressure caused by skeletal muscle contraction. Although the sensations could be

long-lasting, no associated permanent alteration in structure was noted.(4) Pain was most often described as non-pulsatile, distributed bilaterally in occipital, facial, and frontal, or "hat-band" regions.(3) Onset of pain was usually related to exacerbation of life stress.(4)

New criteria for migraine headache are currently being developed and are likely to circulate in the spring of 1988. The major difference between the new and current definition involves the addition of periodicity of migraines to further differentiate them from tension headaches and temporal-mandibular joint syndrome. In order to be classified as having migraine, the patient must experience headache-free periods, have no more than a specific number of headache episodes per year (approximately 12), and each headache must not last greater than 24 hours.(5)

The wide disparity of migraine definitions is partially attributable to the lack of objective diagnostic tests for migraine. Therefore, information regarding migraine is derived from a clinical interview based upon the subject's description of symptoms. A similar situation pertains to psychiatric diagnosis as well. According to Robins and Guze (6), there are five phases necessary to establish a valid psychiatric classification, and these criteria can be extended to apply to diagnoses in medicine. The first phase is clinical description. Clinical description comprises not only the symptomatology but also the epidemiology which distinguishes one disorder from all others.

Migraine literature abounds with careful portrayals of the clinical features of migraine as well as broad community studies to delineate the epidemiologic parameters of the affected population.

The second factor necessary for a valid diagnostic category is delimitation from other disorders. In order to study a specific disorder, the probands should be clinically homogeneous; subjects with other disorders with similar clinical manifestations to that under study should be carefully excluded. With migraine, the diagnosis may be one of exclusion, following diagnostic tests to rule out diseases with overlapping symptoms. One advantage to utilizing patients in treatment for migraine to study the illness is that most doubtful cases will therefore be excluded from the group. The third phase, that of laboratory study, is less adequately established for migraine. Research to explain the pathophysiology of migraine remains inconclusive, and there are no chemical, radiological or anatomical findings to separate migraine from other headaches. The fourth and fifth phases are follow-up study and family study. The former establishes that over time, the patients do not have widely disparate outcomes or develop another disorder which could have caused the migraine-like manifestations. The latter proposes that since many diseases run in families, showing increased rates of migraine in a proband's relatives helps confirm diagnostic validity.

The following discussion of migraine is loosely structured

along the five diagnostic phases described by Robins and Guze.(6) The literature involving the first three steps toward establishing a valid diagnostic category for migraine--clinical description, delimitation from other disorders and laboratory study--is reviewed in three separate sections. The last two phases--follow-up and family studies--are included in the broader category of epidemiology. Additionally, specific aspects of migraine, psychopathology, endocrinology and their interrelationship will be explored in detail.

Clinical Description and Classification

Most researchers divide migraine headaches into "classic" and "common" varieties. The "classic" sub-type accounts for 10% to 15% of all patients with migraine.(7,8) A sharply-delineated prodrome usually precedes the actual headache by approximately twenty minutes and resolves with the onset of pain.(8) The neurologic manifestations of the prodrome include visual, motor and sensory disturbances.(4) Visual auras predominate, characteristically with a scintillating scotoma or "fortification spectrum." A central or paracentral cluster of strobing-neon, zig-zag lines coallescing into a serrated shape resembling a fort's embattlements slowly travels across the visual field. The scotoma enlarges and distorts as it moves toward the edges of the visual field, and eventually disappears.(8,9) The headache phase of "classic" migraine is typified by unilateral, pulsatile pain,

photophobia, and alimentary disturbances such as anorexia, nausea and vomiting.(7,10)

Although the "common" and "classic" variants of migraine share much of the same symptomatology, the prodromes of "common" migraine are less well-defined, often preceding the actual headache by hours or days.(7) These "common" migraine prodromes, often comprised only of mood changes such as depression, elation or irritability, may only precede the headache phase 25% of the time.(11) The actual headache of the "common" type is less likely to be unilateral than in "classic" migraine and often lasts longer than the headache of "classic" migraine.(7) The Ad Hoc Committee noted the relationship of "common" migraine to alterations in the environment, occupational exposure and menstruation. Reflecting these associations, "common" migraine has often been referred to as "atypical migraine" or "sick headache."(4)

These two major divisions of migraine are not mutually exclusive, however. An individual with a past history of "classic" migraine may present with "common" migraine, or even a headache with features of both. Most migraine sufferers also have experienced muscle-contraction headaches, further confusing classification attempts.(7)

Delimitation from Other Disorders

When vascular headaches were first elucidated, "cluster"

headaches and migraine were described as differing manifestations of the same entity. "Cluster" headaches consist of unilateral facial or head pain of brief duration occurring at least once per day over the course of weeks or months. These intense headaches, lasting less than two hours, remit for long periods of time only to recur with equal furor. Lacrimation, rhinorrhea and conjunctival injection frequently accompany the headache. Twenty percent also demonstrate an ipsilateral Horner's Syndrome, ptosis, miosis, enopthalmus and anhidrosis.(4,5)

Recently, however, most scientists have concluded that "cluster" headaches and migraine are two separate classes of headache. "Cluster" headaches occur more commonly in males, demonstrate different serum levels of histamine and serotonin, and have a disparate time course and frequency than migraine.(9) "Cluster" headaches, therefore, have been excluded from most current migraine research.

One additional form of vascular event, recently described as "late-life migraine" closely simulates a transient ischemic attack and appears in a separate epidemiologic pattern from other varieties of migraine. Patients tend to be 50 to 60 years of age and 35% have had no previous migraine headaches. Symptoms consist of migrainous manifestations such as scintillating scotomas and paresthesias, but 60% have no associated headache. These symptoms last approximately 15 to 20 minutes, and the re-occurrence of identical episodes helps to rule out an embolic etiology. "Late-life migraine" is a diagnosis of exclusion

following normal angiography and results in no permanent neurologic deficits.(12) The relationship of "late-life migraine" to "common" and "classic" migraine is unknown, and therefore these patients are not usually considered as part of the group of migraineurs.

Other syndromes mimic migraine symptomatology and must be considered as part of the differential diagnosis. Cerebral ischemia, tumor and epilepsy may present with neurologic manifestations similar to those of migraine. More obscure diseases such as pheochromocytoma and temporal arteritis have also been mistakenly classified as migraine.(7) These potentially fatal illnesses have been recognized as possible etiologies of migraine-like symptoms and are carefully excluded prior to designating a patient as a migraineur.

Epidemiology

Researchers estimate that 4-19% of adult men and 8-29% of adult women suffer from some form of migraine headache.(13,14) In absolute terms, the National Migraine Foundation states that there are 12 million migraine sufferers in the United States alone. Less than 50% of these seek medical assistance, resulting in a patient self-selection bias for the more severe clinical manifestations.(14) The onset of migraine headaches may occur from the childhood years through adulthood (7), with the mean age of onset between 5 and 11 years of age.(14) Selby and

Lance documented first episodes of migraine occurring as early as 18 months of age and as late as 60 years of age.(15) Lifetime prevalence of migraine increases with age, peaking in males during the fourth decade and in females during the late fourth or fifth decade of life.(10) Ninety-two percent of the 496 patients evaluated by Selby and Lance had onset of migraine headaches prior to age 40, with 21% prior to age 10.(15)

Childhood migraine, however, may be underestimated due to misdiagnosis. Many children who later manifest the complete migraine syndrome present earlier with gastrointestinal and neurologic precursors without head pain. Motion sickness, cyclic vomiting, unilateral paralysis and visual symptoms have all been correlated with future migraine onset.(7,8) Migraine has even been missed in younger patients complaining of headache. A recent JAMA article reported that adolescent females may be accused of alcohol or drug abuse when in reality they have a migraine varient involving the basilar artery. The patient appears intoxicated, with dizziness, dysarthria and blurred vision.(8) MacDonald evaluated 421 children under the age of 15 who presented to an outpatient clinic with headache.(16) Although tumors, seizures, depression and tension headache were eventually diagnosed in some patients, the majority were classified as migraineurs.

Table 1. Diagnosis in 421 Children with Headache (16)

Diagnosis	Male N	Male %	Female N	Female %
Migraine Headache				
Classic	54	(24.3)	39	(19.6)
Common	85	(38.3)	66	(33.2)
Hemiplegic	8	(3.6)	6	(3.0)
Ophthaloplegic	1	(0.5)	0	(0.0)
Basilar Artery	7	(3.2)	9	(4.5)
Acute Confusional State	2	(0.9)	0	(0.0)
+ Tension Headache	20	(9.0)	24	(12.1)
+ Seizures	5	(2.3)	6	(3.0)
Tension Headache	19	(8.6)	26	(13.1)
Depression	2	(0.9)	8	(4.0)
Seizures	6	(2.7)	9	(4.5)
CNS Tumor	3	(1.4)	1	(0.5)
CNS Vascular Malformation	1	(0.5)	1	(0.5)
Other	9	(4.1)	4	(2.0)
Total	222		199	

As suggested by MacDonald's study, the pre-pubertal incidence of migraine is similar for both sexes.(17) At some point during the second to early third decades, however, migraine incidence demonstrates a difference between the sexes.(14) (see Table 2) As many as four to eight times the number of adult females as compared to adult males may experience migraine headaches.(17)

Table 2. Lifetime Prevalence of Migraine in Schoolchildren (18)

Age (years)	Migraine (%) Boys	Girls
7	1.1	1.7
8	2.7	2.7
9	3.5	2.9
10	4.0	3.3
11	3.7	5.7
12	3.5	6.9
13	4.0	5.9
14	5.4	4.8
15	1.5	8.2

Although careful epidemiologic study verifies the female preponderance in migraineurs, correlations with intelligence and socio-economic status have not withstood similar tests.(13) Waters (19,20) and Bille (18) reached separate, but similar, conclusions following community studies of adults and children with migraine. The increased prevalence of highly intelligent, professional, middle and upper class migraine patients reflects a self-selection or investigator bias. Migraine sufferers with these characteristics are more likely to obtain medical help than their lesser educated and poorer counterparts.

Twin studies have also been an invaluable epidemiologic tool for evaluating possible genetic or familial influences in migraine. Although controlling for environmental influences remains difficult, increased concordance ratios of migraine in monozygotic versus dizygotic twins implies a role for genetic transmission in migraine.(14) Lucas (21) evaluated 1300 twins registered by the Institute of Psychiatry in London and concluded that both twins had migraines in 26% of monozygotic pairs and 13% of dizygotic pairs. This statistically significant difference supported earlier studies by Harvald and Hauge (22), and Ziegler et al. (23) stating zygosity disparities of 33% versus 5.3% and 22% versus 7%, respectively.

Pathophysiology and Laboratory Study

Whereas most researchers agree that migraine headaches are

genetically influenced, the pathophysiology of migraine remains a hotly debated issue. There have been two major hypotheses advanced, and neither irrefutably proven. Both the vascular and neural theories retain broad-based support, and many believe that the true pathophysiology contains elements from each.

One of the earlier proponents of the vascular theory was Harold G. Wolff, Chairman of the Department of Neurology at Cornell Medical School. During the 1930's and 40's, Wolff induced migraines in patients during craniectomy and noted the resultant hyperemia. He also observed that the migraine-associated visual disturbances ceased when patients inhaled a potent vasodilator, such as amyl nitrate.(9) Combining these results, Wolff concluded that intracerebral vasoconstriction caused the preceding aura of migraine and triggered extracranial vasodilatation which corresponded to the headache phase.(9)

Since Wolff put forth the vascular theory of migraine headache, his original ideas have been embellished, but the concept remains essentially unchanged. The migraine cycle commences with a rise in plasma norepinephrine. Increased norepinephrine leads to platelet aggregation. The platelets, in turn, release serotonin and ADP, causing additional platelet aggregation, arterial constriction and capillary dilatation. The decreased blood flow and cerebral ischemia due to arterial constriction result in the prodromal aura of neurologic and visual disturbances.(8,9)

In addition to serotonin, aggregated platelets also release

neurokinins. These sensitize pain receptors in extracranial vessel walls, accounting for the scalp and neck tenderness which often accompanies migraine headaches.(8,9) Plasma serotonin levels eventually decrease through uptake by perivascular tissue and blood vessels. Arteries then dilate, and the already sensitized blood vessel walls cause the headache phase of the migraine attack.(8,9)

Supporters of the vascular hypothesis cite the pulsatile quality of the headache as well as the relief of symptoms following internal carotid artery compression as proof of Wolff´s theory.(9) Migraine head pain also appears to follow the course of the external carotid artery, and not the trigeminal nerve. The prodromal aura, purportedly caused by cerebral vasoconstriction, is lengthened by alpha agonists such as ergot, and shortened by vasodilators such as nitrates. The painful vasodilatation phase, on the other hand, is relieved by ergot and exaccerbated by nitrates.(24)

The vascular hypothesis, however, fell into disfavor during the late 1970´s and early 1980´s with the advent of renewed enthusiasm for the neural theory of migraine pathophysiology. Only the work of John Sterling Meyer, Professor of Neurology at Baylor, stands out in support of the vascular hypothesis during the 1980´s. Meyer studied 324 patients with vascular headache using Xenon-133 inhalation methods. This prospective trial examinined patients during the course of a non-induced migraine attack. Meyer found that 74% of "classic" migraines and 67% of

"common" migraines were associated with significant hyperemia during the headache phase of the attack. Meyer contends that this proof of increased cerebral blood flow supports the vascular etiology of migraine headaches.(8)

The neural hypothesis, as first stated by Liveing in 1873 (25), proposed that a primary alteration in cerebral function caused the migraine headache, and vascular change was only a secondary accompaniment. This theory regained popularity when researchers noted puzzling disparities between areas of altered cerebral blood flow and distribution of migraine symptomatology. The headache phase of migraines is often unilateral, yet the observed vascular dilatation occurs bilaterally. The vasoconstrictive phase, on the other hand, often spreads anteriorly from the occipital lobe, crossing arterial anatomical boundaries, but not the midline.(24)

Research upholding the neural theory spans the course of a century. From 1890 and the work of Roy and Sherrington (26) to Sokoloff's study in 1978 (27), scientists have demonstrated that vascular calibre changes as a direct consequence of focal metabolic change. Lance et al. in 1983 (28) showed that direct neuronal stimulation results in alterations of cerebral circulation. Using electrodes, Lance stimulated the locus ceruleus in monkeys and noted the onset of intracerebral vasoconstriction as well as extracerebral vasodilatation. Applying these same techniques to cats, Lance proved that trigeminal nerve stimulation caused external carotid artery

dilatation.(28)

The most definitive experiments propounding the neural hypothesis come from Jesse Oleson's lab in Denmark during the early 1980's. Oleson et al. measured cerebral blood flow using Xenon-133 inhalation and photon emission tomography during naturally occurring migraine attacks. Differentiating between "common" and "classic" migraineurs, Oleson found no alteration in cerebral blood flow in twelve patients with "common" migraine headache. Three out of eleven "classic" migraine sufferers also showed normal perfusion. The remaining eight patients with "classic" migraine demonstrated an area of decreased blood flow unilaterally. The low-flow regions corresponded to an approximate 17% decrease in perfusion and was located on the lateral aspect of the side contralateral to the neurologic manifestations. At no point was increased perfusion observed, and, in fact, the relative oligemia persisted four to six hours into the headache phase.(29)

Prior to these experiments, this same group of researchers observed the pattern of hypoperfusion resulting from angiographically-induced "classic" migraine. The oligemic region progressed anteriorly as a spreading wave at 2mm/minute. The area of hypoperfusion did not traverse either the central or lateral sulci, and reduced CO_2 activity and abnormal cortical activation were noted throughout the oligemic region.(30,31) Oleson and Lauritzen likened this progressive wave of hypoperfusion to the so-called Spreading Depression of Leao.(29)

Leao originally described the cortical response to noxious stimuli in 1944. Following electrode stimulation of the cerebral cortex of rabbits, Leao recorded a brief surge in neuronal activity which lasted five to ten seconds. This was followed by decreased or "depressed" activity which spread outward at a rate of 3mm/minute and did not regain normal activity for five to ten minutes.(32) Concomitantly, Leao noted a 50 - 100% increase in pial artery diameter arising immediately in the wake of the spreading wave of depression. This dilatation lasted 1.5 to 3 minutes and was followed by a longer period of slight vasoconstriction.(33) More recent experiments have shown that the earliest ionic disturbance associated with spreading depression is an increase in extracellular K^+.(34) This has led some to hypothesize that a hypoxic event might result in increased extracellular K^+ levels triggering a wave of spreading depression.(8)

Moskowitz (35) expanded upon the similarities between the hypoperfusion pattern of migraine and the Spreading Depression of Leao by examining the role of Substance P. Substance P, a peptide located in primary sensory neurons, affects vascular calibre and permeability. Using radioimmunoassay, Moskowitz examined multiple laboratory animal species and discovered high levels of Substance P in pial arteries, the same vessels that Leao noted dilated following the wave of depressed neuronal activity. By directly applying Substance P onto cerebral vessels, Moskowitz found resultant vasodilatation. Substance P

also has other actions such as mast cell degranulation and disruption of the blood-aqueous barrier in the eye.(35) Although the connection between migraine pathophysiology, the Spreading Depresssion of Leao and Substance P remains largely controversial, the concept that the observed oligemia associated with migraine is secondary to a disruption in the cerebral neural elements continues to be central to the neurogenic hypothesis of migraine etiology.

Treatment

The disagreement surrounding migraine pathophysiology is reflected by the disparate treatment modalities advocated. Mild migraine headaches often respond to aspirin or a combination of aspirin and metoclopramide, a dopamine antagonist which increases gastrointestinal motility and effectively raises aspirin absorption.(36) More severe episodes require stronger abortive therapy. Ergotamine tartrate, a peripheral vasoconstrictor acting through alpha adrenergic stimulation, has long been the treatment of choice for acute attacks. When taken during the prodrome or early after the advent of pain, ergotamine is effective in 80 - 90% of migraineurs.(37) Ergotamine use is limited by such adverse side effects as nausea, vomiting and vasospasm, possibly leading to claudication, gangrene and cardiac ischemia.(36,37,38) Drug dependency and increased headache may also result after long periods of high dosages. Dopamine,

propranolol, erythromycin and troleandomycin all may enhance the potentially serious side effects of ergotamine.(36,37) Nonsteroidal anti-inflammatory agents, though not yet approved by the U.S. Food and Drug Administration, have also been shown to be effective in the treatment of migraine. Recent studies have shown NSAIDs to have greater efficacy than placebo or ergotamine.(39,40)

Prophylactic medication is recommended for frequency or unresponsiveness to abortive therapy. The most widely prescribed prophylactic agent is propranolol, a non-specific beta adrenergic antagonist. Although the exact pathway of action is unknown, postulates include propranolol's inhibition of vasodilatation and prevention of cortical arteriolar spasm.(37)

Those headaches refractory to all other medications may be prevented by methysergide. A semisynthetic ergot alkaloid, methysergide use is restricted by such deleterious side effects as weight gain, peripheral edema, and subendocardial, pleuropericardial and retroperitoneal fibrosis.(36) Methysergide's prophylactic mechanism is thought to be related to its actions as a peripheral antagonist and central agonist of serotonin.(37) Tricyclic antidepressants, calcium-channel blockers, monoamine oxidase inhibitors, and anti-estrogens all have their own proponents.(9,36,41,42,43) The "common" migraine subtype "menstrual migraine" even has its own prophylactic drug or choice--naproxen, a nonsteroidal anti-inflammatory drug.(44) Though efficacy is largely anecdotal, a few well-controlled

studies have been performed.

Table 3. Response to Migraine Prophylaxis

Agent	Patients with >or= 50% Improvement
Nimodipine	69.0%
Methysergide maleate	58.3%
Amitryptyline	55.3%
Propranolol	51.6%
Pizotifen	50.9%
Clonidine hydrochloride	40.9%
Placebo	34.0%

Adapted from Gelmers (9) and Couch and Hassanein (41).

Patients with migraine have been reported to respond to placebo in 20 - 40% of cases.(9) Some researchers, therefore, have focused on nondrug intervention. Behavioral modification techniques including repetition of autogenic phrases, electromyographic biofeedback and thermal biofeedback all have been utilized with some benefit. When Sargent et al.(45) compared these methods to a "no treatment" control group, a statistically significant improvement in migraine headaches was found. The placebo effect of behavioral modification versus non-treatment, however, could not be well-controlled.

The theory behind behavior-related therapy is that migraines may occur more frequently during stressful periods or mood changes. Levor et al.(46) evaluated 33 migraineurs and concluded that although the migraine sufferers were exposed to stress levels similar to the general population, they were more likely to respond to routine stress with an acute migraine attack. The

migraineurs experienced an increase in stressors over a four daycourse preceding and including the day of a migraine headache. Using self-ratings, Harvey and Hay (47) analyzed mood changes in eight migraine patients. This preliminary prospective study revealed that migraine patients had reduced depression and an increased level of alertness on days immediately prior to headache days.

In addition to stress, multiple external triggers for migraine headaches have been cited in the literature, with little scientific substantiation. Seasonal and temperature changes as well as exposure to flickering lights have been proposed as migraine stimuli. Dietary causes such as monosodium glutamate, alcohol and foods high in tyramine content are frequently blamed. These include such diverse items as chocolate, aged cheese, beer and yogurt.(14,15)

The "Migraine Personality" and Psychopathology

Clinicians have often noted that persons suffering from migraine seem to exhibit a particular constellation of personality traits consisting of perfectionism, excessive drive and meticulousness. (38) The concept of the "migraine personality" implies that migraineurs have a specific combination of personality traits on which they can be distinguished from persons without migraine.(48)

Studies investigating the link between migraine and

personality have taken two forms. Observational and psychoanalytical reports utilize no objective data, but represent an aggregate of a specialist's experiences with migraine patients. Empirical research uses questionaire and self-report inventories. An individual's responses are then correllated with specific psychiatric diagnoses. If the latter is community rather the clinically based, possible self-selection bias for more serious cases or specific socio-economic characteristics will be obviated.

Early observational studies by Wolff (49) and Alvarez (50) noted that migraineurs were perfectionists. Touraine and Draper (51) and Furmanski (52) stressed anxious qualities. Migraine patients were described as defensive by Mitchell and Mitchell (53) and as repressing hostilities by Kolb (54) and Friedman and Merrit (55). Sacks (56), however, found no composite personality common to migraineurs. The applicability of these reports is limited by their differing definitions of migraine, lack of control groups, and absence of quantitative analysis.(14)

Empiric research, though, noted many of the same characteristics. Utilizing self-administered questionaires, Bille (57) concluded that children with migraine were more likely to be anxious and tense, and Bildhorff et al.(58) stated that adult migraineurs were more inhibited and compulsive. Maxwell (59) ascertained that clinic patients with migraine were more neurotic according to the Maudsley personality inventory than patients without migraine. Using the Jackson Personality

Inventory, however, Schmidt et al. (48) found no evidence supporting the above traits, but did find that migraine sufferers scored lower on scales measuring complexity, risk taking and social participation. Others, such as Lucas (21), Davis et al.(60), and Henryk-Gutt and Rees (61) identified no reproducible "migraine personality."

The most consistently cited association with a specific psychiatric disorder is the link between migraine and depression. Studies elucidating this association have focused primarily on migraineurs (15,62,63), patients with depression (64,65,66), or random community samples (67,68). Although most substantiate the correlation between migraine and either depression or anxiety, they differ widely in magnitude, sex disparities and individual symptom patterns noted. Once again, the inconsistencies may be attributed to different definitions and measurement of migraine and psychopathology as well as sample bias.

Co-occurrence of two disorders is further evidenced by efficacy of one drug class in treating both diseases and family psychiatric evaluations to explore genetic transmission. As previously stated, tricyclic antidepressants and monoamine oxidase inhibitors have proved beneficial for some migraine patients. Well-controlled studies, however, are scarce. Familial transmission of both migraine and depression was recently investigated by Merikangas et al.(69) They evaluated a group of 133 patients with major depression, a group of 82 normal controls and 400 interviewed first-degree relatives of the

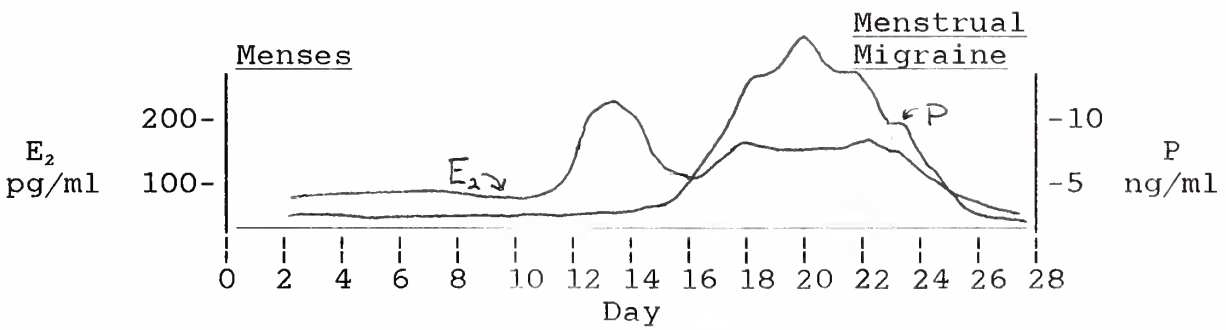
probands and controls. After controlling for the effects of age and sex, patients with depression had a significantly greater prevalence of migraine than those without depression (relative risk = 2.4). Although both migraine and depression were familially transmissible, their association was not demonstrated to be genetically influenced. Merikangas et al. therefore proposed that depression could either be a sequela of migraine or the diathesis resulting in both.

"Menstrual Migraine"

The postulated relationship between migraine and depression raises the question of a possible link between "menstrual migraine" and the premenstrual syndrome. Some researchers associate the proportionally increased rate of migraine in pubertal and post-pubertal females with a specific subset of migraine dubbed "menstrual migraine." Approximately 60% of female migraineurs correlate migraines with their menstrual cycle, usually immediately preceding or during menses.(17) The strict definition of "menstrual migraine," however, is that of "common" migraines coinciding with the week preceding or the week of menstruation. The woman with true "menstrual migraine" will never have migraines outside of the paramenstrual period. Digre and Damasio (44) applied this rigid definition to a group of migraineurs and concluded that 8% of women with migraine have "menstrual migraine." Trends within the group of women with

"menstrual migraine" include migraine onset with menarche, a tendency toward remission with menopause, and decreased frequency during pregnancy.(17) Between 60% and 80% of women evidence gestational improvement, especially during the second and third trimesters.(3,17) Estrogen levels rise with pregnancy and fall with menopause, but during both, the cyclic change in estrogen associated with menstruation is absent. This observation triggered the hormonal hypothesis that the relative cyclic change in estrogen levels, and not the absolute value, may be a migraine stimulus.(17) (see Figure 1)

Figure 1. Cyclical Changes in Estradiol and Progesterone (70)



Welch et al. (71) demonstrated that estrogen increases vascular adrenergic receptor production, decreases norepinephrine reuptake and inhibits norepinephrine degradation. Welch hypothesized that under normal conditions, these changes balance each other for no net effect. With the cyclical drop in estrogen, though, the second two actions decrease, and the unopposed extra adrenergic receptors cause severe

vasoconstriction. Compensating homeostatic mechanisms reacting to ischemia lead to vasodilatation and "menstrual migraine."

Another factor implicating hormone levels in migraine etiology is the correlation between oral contraception and increased migraine frequency. Some women date the onset of their migraines to several months following starting birth control pills. Furthermore, in those women who have migraines while using oral contraceptives, almost 70% note decreased frequency of migraines with cessation of the pill.(17) The premenstrual fall in estrogren is even greater with estrogen-containing oral contraceptives than in the normal cycle, additionally supporting the hypothesis that "menstrual migraines" are triggered by relative changes in estrogen level.(71) These trends of "menstrual" or "hormonally-induced" migraine remain contested in the literature, though, and certainly do not hold true for all female migraineurs. A follow-up study by Whitty and Hockaday of 40 female patients with migraine evidenced no overall decrease in migraine frequency with menopause. Approximately equal numbers of women reported an increase in migraines as those who noted decreased or unchanged frequency.(72)

Late Luteal Phase Dysphoric Disorder

Late Luteal Phase Dysphoric Disorder (LLPDD), often previously termed Premenstrual Syndrome, is a proposed diagnosis listed in DSM IIIR. (73) The diagnosis encompasses a range of

emotional and behavioral disturbances associated with the last week of the luteal phase of the menstrual cycle. For most women, this period coincides with the week prior to menses, and lasts no longer than a few days following the advent of menses. This is the same time period as that of "menstrual migraine." Late Luteal Phase Dysphoric Disorder is applicable only to the woman suffering social or occupational impairment with most of her cycles during the course of a year. The symptoms must also remit within a few days of the start of the follicular phase, thereby excluding late luteal phase worsening of existing psychopathology such as Major Depression or Panic Disorder. Because of discrepancies involving retrospective diagnosis, daily self-ratings throughout two symptomatic cycles are necessary prior to assigning the diagnosis.

Figure 2. Diagnostic Criteria for LLPDD (73)

A. Symptoms listed in section B occurred during the last week of the luteal phase and ended within a few days of the start of the follicular phase of the menstrual cycle.

B. At least one of either (1), (2), (3), or (4), and at least five total of the following:

(1) marked affective lability
(2) persistent anger or irritability
(3) anxiety or tension
(4) depressed mood, hopelessness or self-deprecation
(5) decreased interest in usual activities
(6) lack of energy
(7) difficulty in concentrating
(8) change in appetite
(9) change in sleep patterns
(10) physical symptoms such as breast tenderness or swelling, headaches, sensation of "bloating," or weight gain.

C. These changes interfere with work or usual activities and

interpersonal relations.

D. This is not merely an acceleration of an underlying disorder such as Major Depression, Panic Disorder, Dysthymia, or a Personality Disorder.

E. Confirmation by prospective daily self-ratings during at least two symptomatic cycles.

Frank first described premenstrual changes in 1931 (74). He noted tension, seizures, asthma, cyclic edema and subcutaneous hemorrhages in fifteen women 7 - 10 days prior to menses. Frank ascribed these symptoms to "excess circulating levels of female sex hormone."(74) Although much research has followed his original observations, most etiological hypotheses remain based upon the concept of altered gonadal steroid levels. Proposed disturbances include decreased estrogen levels due to reduced renal and hepatic clearance or increased production, and changes in the ratio of estrogen to progesterone secondary to progesterone deficiency (75). Scientific research, however, has not clarified the controversy. Of ten studies reviewed by Rubinow and Roy-Byrne (75), five reported decreased progesterone during the late luteal phase, one revealed increased progesterone early in the luteal phase, and three found normal progesterone levels. Similar disparities abound in studies of estrogen levels in those with premenstrual syndrome. All of this research, however, measures peripheral hormone levels, which may or may not correspond to fluctuations in the central nervous system. In a review of endocrine theories of PMS, Strickler (76) concluded that some interaction between hormones and neurotransmitters such

as endogenous opiate peptides or catecholamines was the most likely cause for PMS. To support his hypothesis, Strickler cited the covarience of plasma estrogen and endorphin. He also noted that many of the symptoms of PMS such as anxiety and agitation are associated with raised endorphin levels. Therefore, not only do the time courses of "menstrual migraine" and LLPDD overlap, but their postulated etiologies are based on similar mechanisms of cyclical endocrine change and neurotransmitter disturbance.

Proposal

Studies examining the association between depression and premenstrual syndrome have been limited either by small sample size, lack of control group, or retrospective diagnosis of PMS.(77) Although flawed by study design, each did report increased occurrence of depression with PMS. One of the diagnostic criterion for Late Luteal Phase Dysphoric Disorder is headache, although not specifically migraine.(73) Can these associations between headache and LLPDD and LLPDD and depression account for the relationship between migraine and depression? If so, differing rates of depression may be observed in "menstrual migraine" compared with other forms of migraine. Also, the type of depression may be disimilar. Halbreich(78) states that women with LLPDD more frequently experience atypical depression, anxious-agitated depression and hostile depression.

This study investigates the association between migraine

headaches and psychopathology in a sample of men and women in treatment for migraine. Within the group of migraineurs, patients will be subdivided by sex and type of migraine--"classic" or "common." The subgroup of women with "menstrual migraine" will also be individually analyzed and compared for increased rates of depression or specific subtypes of depression. Therefore, if the rate of depression is greater in patients with "menstrual migraine," not only may we infer that the endocrine system underlies the association noted between migraine and depression, but also that "menstrual migraine" is a separate entity from other forms of migraine.

MATERIALS AND METHODS

The subjects consisted of men and women previously diagnosed as having migraine headaches, and currently in treatment with a neuropsychiatrist. All patients were approached first by their physician, and the study and its voluntary nature was explained to them. If the patient agreed, he or she was then contacted by a researcher trained in psychological assessment and interviewing. The interview session lasted from 1 - 3 hours and consisted of a demographic data and medical history questionnaire, a migraine symptom review (see Appendix A) and the Schedule for Affective Disorders and Schizophrenia (SADS-L), for psychiatric status and diagnosis. The migraine symptom review investigates not only the specific characteristics of the migraine, but also migraine triggers, treatment, associated medical illnesses and family history. Subtype classification of "classic" is assigned if the patient describes a well-defined aura preceding a unilateral headache. All other subjects are "common" migraineurs. "Menstrual migraine" is independently designated if a female patient experiences increased headache frequency or severity either before or during menses.

The SADS-L is a "lifetime" structured interview which records information concerning past and current episodes of illness. Information on signs and symptoms are collected systematically and diagnosis is based on established criteria for 25 adult psychiatric disorders.(79,80,81) The six categories we

utilized are major depression, bipolar disorder, panic disorder, generalized anxiety, obsessive/compulsive disorder and phobic disorder. The research disgnostic criteria for each is presented in Appendix B. Statistical significance for this study was determined by using chi-square analysis for categorical responses and t-test evaluations for those questions with a range of possible responses.

Additionally, each proband received a self-assessment package to return at his or her convenience. This report package contained the Maudsley Personality Inventory (MPI, Eysenck), the Dimensions of Temperament Scale (DOTS, Lerner), the Social Adjustment Scale - Self-Report (SAS-SR, Weissman) and the Symptom Checklist 90 (SCL-90, Derogatis). During that same interview, a family pedigree was obtained and Family History Questionnaires were reviewed for each first-degree family member (i.e. parents, siblings and children). Although all of these indices were not utilized for this investigation, they remain available for future analyses.

RESULTS

The migraineurs interviewed consisted of 11 (15%) males and 60 (85%) females. They range in age from 16 to 73, with a mean age of 39. Demographic data reveals a racial distribution of 99% white and 1% black. The mean level of education for the group is college, with the least educated a junior high school graduate, and the most educated holding a graduate or professional degree. 61% are married, 15% divorced, 1% widowed and 23% have never married. Demographic data is summarized in Table 4.

Migraine sub-types were classified by the following procedure: if the patient described a definite migraine prodrome, and the headache was always unilateral and never bilateral, then the proband was assigned to the "classic" migraine group. All others were called "common" migraineurs.

The determination of "menstrual" migraine was independent of the "classic" versus "common" division. Women with "menstrual" migraine were those who responded positively to the question, "Does menstruation seem to trigger your headache?" Only those who specified either "pre" menstruation or "during" menstruation were counted as positive answers.

According to these standards, the interview group consisted of 27 (38%) "classic" and 44 (62%) "common" migraineurs. The average age of onset for all subjects was 16.8 years, with a range of 2 - 45 years (see Figure 3 for distribution). The average migraine was described as causing moderate impairment and

lasting 23 hours. 73% had a family history of headache, and 76% also suffered from tension headaches. The female migraineurs were asked specific questions regarding worsening headache and the menstrual cycle. These data are summarized in Table 5.

The mean age of onset of migraine in "classic" and "common" migraine patients was 16.7 and 16.9, respectively, and is compared by t-test in Table 6. The migraine severity for both groups is summarized using a t-test in Table 7. The association of tension headaches with "common" versus "classic" migraine is explored in Table 8. Another possible disparity between "classic" and "common" migraineurs was tested in Table 9 by examining the presence of family history of migraine. Migraine severity, association with tension headache and family migraine history did not vary by "classic"-"common" subtype.

Dividing these same probands by the criteria for "menstrual migraine," 37 (53.5%) of the study group were classified as having "menstrual migraine." Two patients could not be assigned because of insufficient information. The same variables--age of migraine onset, severity, tension headaches and family history--were applied to the "menstrual migraine" sub-group in Tables 10, 11, 12 and 13, respectively. Although age of onset and tension headache were not dependent on "menstrual migraine" classification, "menstrual migraineurs" tended to have decreased migraine severity and increased migraine family history, $p=0.076$ and $p=0.070$, respectively.

A synopsis of the psychopathology within the proband group

is displayed in Table 14. This data is analyzed for association with migraine sub-types "common," "classic" and "menstrual migraine" using the chi-square method in Tables 14 and 16. Table 17 shows the results for "menstrual migraine" when comparing only the female migraineurs and Table 18 investigates possible sex disparities in psychopathology. Lifetime prevalence on psychopathology did not vary by sex or "menstrual migraine" classification. Patients with "classic" migraine, however, did tend to have increased rates of panic disorders ($p=0.10$).

Table 4. Demographic Data

Age	Mean 39 years	Range 16-73 years
Sex	15% males	85% females
Race	99% white	1% black
Education	68% college level	
Marital Status	61% married	

Figure 3. Distribution of Age of Migraine Onset

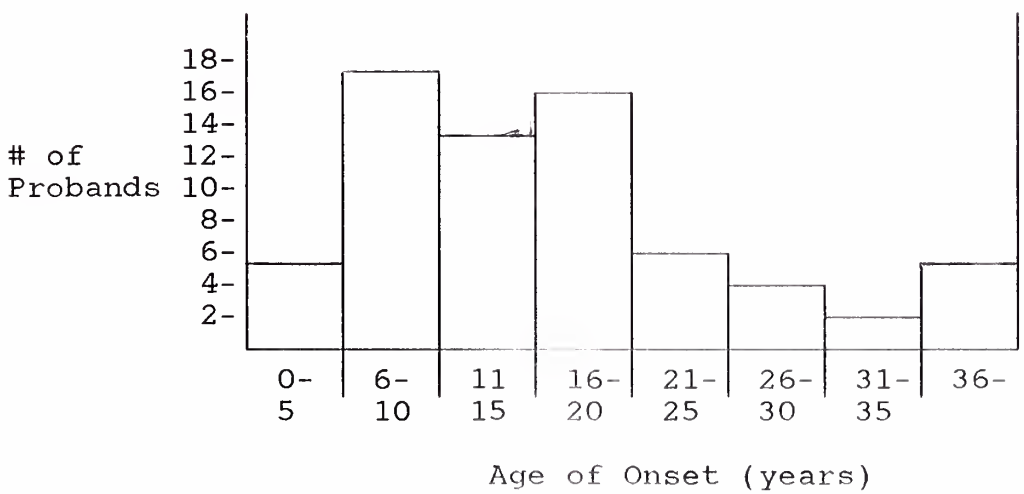


Table 5. Migraine and the Menstrual Cycle

Proportion of subjects with precipitation or worsening of headaches by:

Menstruation	64%
Pregnancy	30%
Childbirth	5%
Post-partum	14%
Menopause	16%

Table 6. "Classic" vs. "Common" Migraine Onset - t-test

	N	Mean Age	Std Dev	Range	T	DF	Sig
Classic	27	16.7	9.3	5-39	0.055	66	N.S.
Common	41	16.9	10.4	2-45			

Table 7. "Classic" vs. "Common" Migraine Severity - t-test

	N	Mean	Std Dev	Range	T	DF	Sig
Classic	27	4.4	1.3	2-6	0.870	69	N.S.
Common	44	4.1	1.7	1-6			

Numerical Correlation of Severity

1. only mild subjective distress, no impairment
2. considerable distress, but no apparent impairment in function
3. mild impairment, primarily in daily activities at home
4. moderate impairment, extending to social and work activities
5. severe
6. extreme, essentially incapacitated and must go to bed

Table 8. Subjects with Tension Headache by Classic-Common Subtype

	Tension Headache Yes	X^2	DF	Sig
Classic	18 (66.7%)	2.109	1	N.S.
Common	36 (81.8%)			

Table 9. Family History of Migraine by Classic-Common Subtype

	Family Headache History: Yes	X^2	DF	Sig
Classic	19 (70.4%)	0.137	1	N.S.
Common	32 (74.4%)			

Table 10. "Menstrual Migraine" Age of Onset - t-test

Menstrual Migraine	N	Mean Age	Std Dev	Range	T	DF	Sig
Yes	36	18.4	9.7	4-45	-1.48	65	N.S.
No	31	14.8	10.0	2-40			

Table 11. "Menstrual Migraine" Severity - t-test

Menstrual Migraine	N	Mean	Std Dev	Range	T	DF	Sig
Yes	37	3.97	1.5	1-6	1.80	67	0.076
No	32	4.63	1.5	1-6			

Table 12. "Menstrual Migraine" and Tension Headache

		Tension Headache: Yes	X^2	DF	Sig
Menstrual Migraine	Yes	30 (81.1%)	0.816	1	N.S.
	No	23 (71.9%)			

Table 13. "Menstrual Migraine" and Family History

		Family History of Headache: Yes	X^2	DF	Sig
Menstrual Migraine	Yes	30 (81.1%)	3.281	1	0.070
	No	19 (61.3%)			

Table 14. Lifetime Prevalence of Psychopathology in Probands and Age of First Episode

Diagnosis	Proband (%)	Mean Age of First Episode (years)
Major Depression	59.2%	27.0
Bipolar Disorder	4.2%	31.0
Panic Disorder	19.7%	24.9
Generalized Anxiety	40.8%	22.1
Obsessive/Compulsive	8.5%	19.5
Phobic Disorder	32.4%	15.3

Table 15. "Classic" vs. "Common" Migraine and Psychopathology

Diagnosis	"Classic" N=27	"Common" N=44	X^2	Prob
Major Depression	70.4%	52.3%	2.268	0.132
Bipolar Disorder	7.4%	2.3%	1.090	0.296
Panic Disorder	29.6%	13.6%	2.704	0.100
Generalized Anxiety	40.7%	40.9%	0.000	0.989
Obsessive/Compulsive	11.1%	6.8%	0.399	0.528
Phobic Disorder	37.0%	29.6%	0.429	0.513

Table 16. "Menstrual Migraine" and Psychopathology

	Menstrual Migraine			
Diagnosis	Yes N=37	No N=32	X^2	Prob
Major Depression	62.2%	59.4%	0.056	0.813
Bipolar Disorder	5.4%	3.1%	0.215	0.643
Panic Disorder	21.6%	18.8%	0.087	0.767
Generalized Anxiety	43.2%	37.5%	0.235	0.628
Obsessive/Compulsive	8.1%	9.4%	0.035	0.852
Phobic Disorder	37.8%	28.1%	0.728	0.393

Table 17. "Menstrual Migraine" and Psychopathology--Females Only

	Menstrual Migraine			
Diagnosis	Yes N=37	No N=21	X^2	Prob
Major Depression	62.2%	52.4%	0.528	0.467
Bipolar Disorder	5.4%	4.8%	0.915	0.915
Panic Disorder	21.6%	19.1%	0.054	0.816
Generalized Anxiety	43.2%	28.6%	1.225	0.268
Obsessive/Compulsive	8.1%	4.8%	0.234	0.629
Phobic Disorder	37.8%	23.8%	1.197	0.274

Table 18. Sex and Psychopathology

Diagnosis	Male N=11	Female N=60	X^2	Prob
Major Depression	72.7%	56.7%	0.992	0.319
Bipolar Disorder	0.0%	5.0%	0.574	0.449
Panic Disorder	18.2%	20.0%	0.019	0.889
Generalized Anxiety	54.6%	38.3%	1.011	0.315
Obsessive/Compulsive	18.2%	6.7%	1.593	0.207
Phobic Disorder	36.4%	31.7%	0.094	0.760

DISCUSSION

Psychiatric disorders within the migraine population did not vary by "common"-"classic" subtype or "menstrual migraine." Patients with "menstrual migraine," however, tended to have less severe headaches and a greater family history of migraine.

The subject population was mainly middle aged, white, highly educated and married. This may reflect the referral source, a medical specialist in private practice. Epidemiologic studies, however, have demonstrated that no correlation exists between socioeconomic status and migraine.(18,19)

The preponderance of females in the sample (5.5 : 1, female:male) exceeds the ratio usually reported of 1.5 - 2 : 1.(14) Our probands, though, are a treated sample and would not be expected to correspond to ratios found through random community surveys.

Therefore, we hope to obviate the bias of a treated sample by comparing prevalence of psychopathology between subdivisions of the entire group. Any comparison to community controls would not be valid because patients under the care of a neuropsychiatrist should have higher rates of psychiatric disorders because of a treatment-seeking bias. Within the sample, all of the patients have had the same self-selection.

In their epidemiologic review of affective disorders, Weissman et al. (82) reported studies showing community lifetime prevalence of nonbipolar depression which ranged from 6 - 18%.

However, Merikangas et al. (69) found a lifetime prevalence of major depression of 35% in community subjects with migraine. The lifetime prevalence of major depression in our treated population is 59.2%. which is approximately double that of the community migraine sample. Furthermore, subjects with anxiety disorders with migraine exhibited a lifetime prevalence rate of 77% as compared to a rate of 53% in non-migraine sufferers. Therefore, although the rate of psychiatric disorders within our study is high compared to random community trials, the disparity is less significant with respect to the general population of migraineurs or migraine patients in treatment for anxiety disorders.

The migraine characteristics for the interview group follow the trends reported in the literature. The average migraine onset was 16.8 years, which is older than that listed by Linet and Stewart (14), but younger that that found by Merikangas, et al. (69) Greater than 50% of the probands experienced their first migraine between the ages of 5 and 17.

Family history of migraine was positive in 73% of our patients. In their review of migraine, Linet and Stewart (14) cited studies showing 10 - 90 % of migraineurs with a positive family history of migraine. The varied definitions of migraine may account for this discrepancy. In our survey, we required only the presence of a recurrent incapacitating headache, and not a formal diagnosis of migraine.

"Common" vs. "Classic"

38% of the study group was classified as having "classic" migraine and 62% as having "common" migraine. Although this is higher than the community-derived figure of 10 - 15% "classic," (7,8) we did utilize a very strict definition to divide the migraineurs. Only those patients with purely unilateral headache and a well-defined prodrome were assigned to the "classic" group. We did, however, classify patients according to the description of their symptoms. This may not always reflect the actual characteristics of the headache nor their change over time. Additionally, migraine sufferers often experience a mixture of "classic" and "common" migraines, with one predominating during a specific time period.

Comparing the "classic" and "common" migraineurs, there were no statistically significant differences in age of onset, family history or associated tension headaches. "Common" migraineurs reported tension headaches more than "classic" migraineurs, 81.8% as opposed to 66.7%, but the chi-square probability was 0.146. There was also no significant disparity in the rate of psychiatric disease between the two subgroups, although the "classic" migraineurs evidenced higher rates in all diagnostic categories except generalized anxiety. However, there was a trend toward association between "classic" migraine and panic disorder.

"Menstrual Migraine"

Whereas "classic" migraine was rigidly defined, "menstrual migraine" was not. 64% of the females linked precipitation or increased severity of migraine to the time either before or during menses. These women were then considered "menstrual migraineurs." This value far exceeds that reported by Digre and Damasio (44) of 8%. However, they included women who solely suffered from migraines during the paramenstrual period and were headache-free the remainder of the month, whereas those subjects from the present study were unselected for this condition. The other questions regarding migraine and the menstrual cycle elicited expected results. 30% of the women who had been pregnant experienced more migraines during pregnancy. This observation is consistent with the findings of research demonstrating first trimester worsening and second and third trimester improvement of migraine (3,17). 14% of the women in our sample cited post-partum migraine increase, which may imply that their migraines had decreased during the latter part of pregnancy. 16% of the women had worse migraines following menopause, a figure supporting Whitty and Hockaday's claim than migraine frequency does not necessarily decrease with menopause.(72)

Analyzing the "menstrual migraine" data, those with "menstrual migraine" showed a trend toward less severe migraine ($p=0.076$). They also had later migraine onset (18.4 years compared to 14.8 years), although not of statistical

significance. Increased age reflects onset at or following puberty, and not during childhood. "Menstrual migraineurs" demonstrated an increased rate of familial migraine ($p=0.070$), but no difference in associated tension headache. The trends toward less severity and higher rates of familial migraine may signal that "menstrual migraine" is a separate form of headache from the rest of migraine. If these disparities remained significant with a larger sample size, laboratory study to evaluate differing hormonal pathophysiology would be warranted.

There was no correlation, however, between "menstrual migraine" and psychopathology. The data were analyzed first comparing "menstrual migraineurs" with all other probands and then with females, only. There was no real difference between these two methods of comparison, though, because the sex of the patients was not related to the rate of psychopathology.

CONCLUSION

Although there is an enxtremely high frequency of lifetime psychiatric disorders among subjects with migraine, we have demonstrated no association between migraine subtypes and psychopathology. "Classic," "common" and "menstrual migraine" each showed increased rates of psychiatric disease compared to random community samples, but there was no significant disparity between the groups. These results imply that the hormonal changes during the menstrual cycle postulated to worsen both "menstrual migraine" and LLPDD are not responsible for the increased rates of psychopathology observed in migraine patients.

This is not, however, the ideal study to assess the inter-relationship between migraine, LLPDD and psychopathology. Both "menstrual migraine" and LLPDD should be diagnosed prospectively, rather than retrospectively. Retrospective diagnosis may artificially increase the prevalence of each. Patients often correlate headaches or mood changes with menses, but careful daily self-ratings fail to verify this association. Therefore, any research involving "menstrual migraine" and LLPDD should begin with daily self-assessment throughout two symptomatic cycles. The proband should note the presence or absence of headache daily. If any migraines occur outside of the paramenstrual time period, the week preceding and week during menses, the patient would fail to have "menstrual migraine" by

the strictest of definitions. Similarly, the patient would assess daily mood alterations. Because of subtle changes and the variability of patient reporting, a standardized instrument such as that developed by Keye (83) would be appropriate. Following ascertainment that the proband has both "menstrual migraine" and LLPDD, psychological assessment begins with the SADS-L. Additional diagnostic indices may be utilized, including the MPI, DOTS, SAS-SR and SCL-90 or any other recognized psychiatric instrument. These results should be compared with multiple control groups to correct biases inherent in the study. Possible controls include "common" or "classic" migraineurs, female migraineurs, females with tension headaches and females with chronic pain. The last of these would evaluate pain as the cause of psychopathology, and the first three would elucidate the effects of sex and type of headache. Frequent blood samples from all groups coudl be obtained to verify that the probands experience cyclical estrogen and progesterone levels. None of these patients should currently be pregnant, use birth control pills or have undergone menopause.

In order to highlight how changes from the normal cycle of hormones affect migraine, a few of the Migraine Symptom Review questions should be reworded. Currently, the questionnaire asks if the proband´s migraines worsened with birth control pill use, pregancy, childbirth, post-partum, and menopause. Actually, this query should have been phrased, "Do your headaches get better or worse...", since many studies suggest that women experience fewer

migraines during pregnancy and after menopause. Also, the question concerning birth control pills would be more useful if divided into two parts--"Have you ever taken birth control pills?" and, if so, "Were your headaches better or worse while you used BCPs?" This would avoid the confusion of a negative response for both patients who had never taken BCPs and for those whose migraines were not more severe or frequent with BCP use.

This thesis was designed as a pilot study to test further the relation between migraine and psychiatric disorders and our methods for assessing this association. Through analyzing the results of these first 71 interviews, we have discovered ways to make the Migraine Symptom Review a more reliable diagnostic instrument. The Migraine Symptom Review, in its current form, provides useful information regarding "classic" and "common" classification, migraine symptoms, triggers and treatment efficacy. The "menstrual migraine" section, however, could be improved by a prospective disgnostic scheme and rewording of questions concerning change in migraine with lifetime alterations in the menstrual cycle, as noted above. These revisions, in conjuction with analysis of the personality inventories and family history questionnaires already obtained, should yield an in-depth profile of the migraineur, subtype of migraine, psychopathology and the familial transmission of each.

Appendix A

Migraine Symptom Review

1. Have you ever suffered from headaches?

2. At what age did you have your first headache?

3. How often do you have your headaches?
   Daily?
   Weekly?
   Monthly?
   Bi-Monthly?
   Annually?
   Less than annually?

4. Do you tend to get migraines during a specific season?
   Winter?
   Spring?
   Summer?
   Fall?

5. Do your migraines seem to occur during a particular month?

6. Is the particular time of day related to your migraines?
   Morning?
   Afternoon?
   Evening?

7. Have you taken any medication to prevent your migraines?
   Beta-blockers?
   Tricyclic antidepressants?
   Mono Amine Oxidase Inhibitors?
   Lithium?
   Methysergide?
   Calcium-channel blockers?

8. Do you take any medication to treat an acute migraine?
   Narcotics?
   Anti-inflammatories?
   Analgesics?
   Ergotamine?
   Oxygen?

9. What is the most helpful treatment for an acute attack?

10. How long do your migraines usually last

11. Do you have a pre-headache warning?
    Does it consist of:

Visual symptoms?
Nausea?
Weakness?
Numbness?
Dizziness?

12. Is the onset of discomfort gradual?

13. When you have a headache, have you also

a) lost your appetite for food?
experienced nausea?
vomiting?
diarrhea?

b) been unable to expose your eyes to light?

c) had visual difficulties such as
blurring?
teichopsia (showers of light)?
hemianopia (blindness in 1/2 of visual field)?
scotoma (blind spot)?

14. Do you have a family history of migraine?

15. Would you characterize the pain you experience as
Throbbing?
Steady?
Unilateral?
Bilateral?
Extending to neck muscles?
Stabbing?
Bursting?
Squeezing?
Causing scalp tenderness?
Ice pick pain?

16. Would you describe the majority of you migraines as
Only mild subjective distress, no impairment?
Considerable distress, but no apparent impairment?
Mild impairment, primarily in daily activities at home?
Moderate impairment, extending to social and work activities?
Severe?
Extreme, essentially incapacitated and must go to bed?

17. Does any particular situation seem to trigger your headache?
While relaxing?
Does it waken you from sleep?
Does sleep relieve it?
Does it get worse during sleep?
Sleeplessness?
Depression?

Anxiety?
Injury?
Illness?
A life crisis such as marriage, divorce or death?
Stress?
After periods of prolonged stress?
After eating particular foods?
Chocolate?
Chinese food (MSG)?
Hot dogs (nitrate)?
High tyramine foods such as cheese, yogurt, sour cream, chicken liver, fresh baked breads, sausages, nuts, pork, beans, herring, vinegar?
Artificial sweeteners?
Coffee?
Tea?
Other caffeine-containing beverage?
Diet soft drinks?
After drinking alcohol?
Beer?
Wine?
Other alcoholic beverages?
Drug usage?
Smoking?
Weather change? either temperature or humidity
If female:
Menstruation? pre, during or post
Oral contraceptive use?
Pregnancy?
Childbirth?
Post-partum?
Menopause?
Have you had a hysterectomy?

18. Do you have any of the following medical problems?
Heart disease?
Palpitations?
Mitral valve prolapse?
Epilepsy?
Hypertension?
Cerebrovascular disease or stroke?
Asthma?
Hay fever?
Vertigo or dizziness?
Gastroesophageal reflux or hiatal hernia?
Peptic ulcer disease?
Nephrolithiasis?
Arthritis?
Diabetes?
Hypoglycemia?
Hypothyroidism?
Hyperthyroidism?

Tension headaches?
Urinary tract infections?
Raynauds disease (hands or feet turn red, blue or white in response to cold)?
Excercise intolerance?
Skin disease (acne, psoriasis)?
Easy bruising?

Appendix B

SADS-L Criteria for Psychiatric Diagnosis (79,80,81)

Major Depression

A through F are required for the episode of illness being considered.

A. One or more distinct periods with dysphoric mood or pervasive loss of interest or pleasure. The disturbance is characterized by symptoms such as the following: depressed, sad, blue, hopeless, low, down in the dumps, "don't care anymore," or irritable. The disturbance must be prominant and relatively persistent but not necessarily the most dominant symptom. It does not include momentary shifts from one dysphoric mood to another dysphoric mood, e.g., anxiety to depression to anger, such as are seen in states of acute psychotic turmoil.

B. At least five of the following symptoms are required to have appeared as part of the episode for definite and four for probable (for past episodes, because of memory difficulty, one less symptom is required).

(1) Poor appetite or weight loss or increased appetite or weight gain (change of 1 lb. a week over several weeks or 10 lbs. a year when not dieting).
(2) Sleep difficulty or sleeping too much.
(3) Loss of energy, fatigability, or tiredness.
(4) Psychomotor agitation or retardation (but not mere subjective feeling of restlessness or being slowed down).
(5) Loss of interest or pleasure in usual activities, including social contact or sex (do not include if limited to a period when delusional or hallucinating). (The loss may or may not be pervasive.)
(6) Feelings of self-reproach or excessive or inappropriate guilt (either may be delusional).
(7) Complaints or evidence of diminished ability to think or concentrate, such as slowed thinking, or indecisiveness (do not include if associated with marked formal thought disorder).
(8) Recurrent thoughts of death or suicide, or any suicidal behavior.

C. Duration of dysphoric features at least one week beginning with the first noticeable change in the subject's usual condition (definite if lasted more than two weeks, probable if one to two weeks).

D. Sought or was referred for help from someone during the

dysphoric period, took medication, or had impairment in functioning with family, at home, at school, at work, or socially.

E. None of the following which suggest Schizophrenia is present:
   (1) Delusions of being controlled (or influenced), or of thought broadcasting, insertion, or withdrawal.
   (2) Non-affective hallucinations of any type throughout the day for several days or intermittently throughout a one week period.
   (3) Auditory hallucinations in which either a voice keeps up a running commentary on the subject's behaviors or thoughts as they occur, or two or more voices converse with each other.
   (4) At some time during the period of illness had more than one month when he exhibited no prominent depressive symptoms but had delusions or hallucinations (although typical depressive delusions such as delusions of guilt, sin, poverty, nihilism, or self-deprecation, or hallucinations with similar content are not included).
   (5) Preoccupation with a delusion or hallucination to the relative exclusion of other symptoms or concerns (other than typical depressive delusions of guilt, sin, poverty, nihilism, self-deprecation or hallucinations with similar content).
   (6) Definite instances of marked formal thought disorder, accompanied by either blunted or inappropriate affect, delusions or hallucinations or any type, or grossly disorganized behavior.

F. Does not meet the criteria for Schizophrenia, Residual Subtype.

Manic Disorder

A through E are required for the episode of illness being considered.

A. One or more distinct periods with a predominantly elevated or irritable mood. The elevated or irritable mood must be a prominant part of the illness and relatively persistent although it may alternate with depressive mood. Do not include if apparently due to alcohol or drug intoxication.

B. If the mood is elevated at least three of the following symptom categories must be definitely present to a significant degree (four symptoms if mood is only irritable):
   (1) More active than usual--either socially, at work, sexually, or physically restless.
   (2) More talkative than usual or felt a pressure to keep on talking.
   (3) Flight of ideas or subjective experience that thoughts

are racing.
(4) Inflated self esteem (grandiosity, which may be delusional).
(5) Decreased need for sleep.
(6) Distractibility, i.e., attention is too easily drawn to unimportant or irrelevant external stimuli.
(7) Involvement in pleasurable activities without recognizing the high potential for painful consequences, e.g., buying sprees, sexual indiscretions, foolish business investments, reckless driving.
(8) Provocative, obnoxious, arrogant, manipulative behavior, causing difficulty for friends, co-workers, family.

C. Overall disturbance is so severe that at least one of the following is present:
(1) Meaningful conversation is impossible.
(2) Disruption of role function socially, with family, at home, or at work.
(3) Delusions or hallucinations at peak of excited period.

D. Manic features lasted more than one week or were terminated by ECT or medication.

E. At least one episode of illness in which none of the following were present except transiently during the most excited period.
(1) Bizarre or fantastic delusion(s) (including delusions of being controlled or influenced or thought broadcasting) having apparently nothing to do with Mania.
(2) Hallucinations of any type throughout the day for several days or intermittently throughout a six month period.
(3) Auditory hallucinations in which two or more voices discuss the patient, his thoughts or actions in the third person.
(4) At some time during the period of illness had delusions or hallucinations for more than one week in the absence of prominent affective (depressed or manic) symptomatology.
(5) At some time during the period of illness had more than one week when he exhibited no prominent manic symptomatology but had several instances of verbal production that made communication difficult because of a lack of logical or understandable organization (obvious thought disorder).

Panic Disorder

A through E are required for the episode of illness being considered.

A. At least six panic attacks distributed over a six week period for a definite diagnosis and three attacks occuring over a three week period for a probable diagnosis. They must occur at times other than during marked physical exertion or a life-threatening situation, and in the absence of a medical illness that could account for symptoms of anxiety. (Do not include if lasts most of the day or if limited to a circumscribed phobic stimulus.)

B. The panic attacks are manifested by discrete periods of apprehension or fearfulness with at least three of the following symptoms present during the majority of attacks required for definite and two for probable (for past episodes, because of memory difficulty, one less symptom is required).

(1) dyspnea
(2) palpitations
(3) chest pain or discomfort
(4) choking or smothering sensations
(5) dizziness, vertigo, or feelings of unreality
(6) paresthesias (tingling)
(7) sweating
(8) faintness
(9) trembling or shaking
(10) fear of dying, going crazy, or losing control during an attack.

C. Nervousness between the panic attacks.

D. The condition has resulted in either impairment in functioning with family, at home, at school, at work, or socially, seeking or being referred for help from someone, taking medication, or abusing alcohol or drugs.

E. The panic attacks are not limited to an episode of probable or definite Major Depression, Schizophrenis, or Schizo-affective Disorders, nor are they limited to a period of two months prior to, or two months after such an episode.

Generalized Anxiety

A through F are required for the episode of illness being considered.

A. An episode of illness in which relatively persistent generalized anxious mood dominates the clinical picture. The anxious mood may be described as anxious, nervous, jittery, tense, restless, or "uptight."

B. At least one of the following:

(1) Difficulty falling asleep.
(2) Sweating, blushing, dizziness, palpitations, or

shortness of breath.
(3) Muscular tension or tremors.
(4) Persistent worrying about future events.
(5) Fidgeting or inability to sit still.

C. Duration of episode at least two weeks beginning with the first noticeable change in the subject's usual condition.

D. The episode of illness being considered does not meet the criteria for Panic Disorder, Major or Minor Depressive Disorder, Schizophrenia, Schizo-affective Disorders, Briquet's Disorder (Somatization Disorder), Intermittent Depressive Disorder, Labile Personality, Unspecified Functional Psychosis, or Manic Disorder, and was not limited to the two months prior to, or after these disorders.

E. The episode of illness may be superimposed on another pre-existing psychiatric disorder, for example, Alcoholism, Phobic, or Obsessive/Compulsive Disorder. This category should be given as an additional diagnosis only if the anxious mood, by virtue of its intensity of effect on functioning, can be clearly distinguished from the subject's usual condition.

F. When the episode of illness is not superimposed on another pre-existing psychiatric disorder, it must result in either impairment in functioning with family, at home, at work, or socially, taking medication, or seeking or being referred for help from someone.

Obsessive/ Compulsive Disorder

A through C are required.

A. Has obsessions or compulsions which are defined as recurrent or persistent ideas, thoughts, images, feelings, impulses, or movements generally accompanied by a sense of subjective compulsion and a desire to resist the event and usually recognized by the individual as foreign to his personality or nature, i.e., "ego alien."

B. The obsessions or compulsions, or reactions to them, have resulted in either impairment in functioning with family, at home, at school, at work, or socially, taking medication, or seeking or being referred for help from someone.

C. The obsessive or compulsive symptoms do not coincide with an episode of probable or definite Major Depressive Disorder, Schizophrenia, Schizo-affective Disorders, not are they limited to a period of two months prior to, or two months after such an episode.

Phobic Disorder

A through C are required for the episode of illness being considered.

A. Persistent and recurring irrational fears of a specific object, activity, or situation which the subject tends to avoid. Usually the avoidance is recognized as unreasonable. In some cases, however, subjects with Phobic Disorder avoid situations because they anticipate overwhelming anxiety or some other strong emotion, and thereby claim their avoidance is rational. Irrational fears without a tendency to avoid specific situations are not phobias, e.g., most "cancer phobias."

B. The phobic symptom(s), reactions to them, or behavior to avoid them has resulted in either impairment in functioning with family, at home, at school, at work, or socially, taking medication, or seeking or being referred for help from someone.

C. The phobic symptoms are not limited to an episode of probable or definite Major Depressive Disorder, Schizophrenia, or Schizoaffective Disorders, nor are they limited to a period of two months prior to, or two months after such an episode.

Subtypes of Phobic Disorder

(1) Agoraphobia: Fear of leaving familiar setting of the home. Usually there are multiple fears including fears of traveling, crowds, closed spaces, stores, heights, with progressive restriction of activities. Usually associated with Panic Disorder.

(2) Social phobias: Fears of situations involving other people not associated with leaving home. Most common are fears of public speaking, blushing, eating in public, writing in front of others, or using public lavatories.

(3) Simple phobias: Single nonsocial phobias not associated with fear of leaving home. The most common are of animals, particularly reptiles, insects, and rodents.

BIBLIOGRAPHY

1. Steinbeck, J., The Wayward Bus. New York: Viking Press, 1947.

2. Aretaeus Cappadox, Heter Crania. In: Corpus Medicorum Graecorum, edited by C. Hude, vol. 3, p. 37, vol. 4, p. 149. Leipzig: Taubner. Cited in A.P. Friedman, "Overview of migraine," in Advanced in Neurology, vol. 33, edited by M. Critchley et al. New York: Raven Press, 1982.

3. Adams, H.E., Feuerstein, M., and Fowler, J.L. "Migraine headache: review of parameters, etiology and intervention." Psychol Bull 87(2):217-37, 1980.

4. The Ad Hoc Committee on Classification of Headache. "Classification of headache." Arch Neurol 6:173-6, 1962.

5. Merikangas, K.R. Personal correspondence.

6. Robins, E. and Guze, S.B. "Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia." Amer J Psychiat 126(7):983-987, 1970.

7. Friedman, A.P. "Overview of migraine." In: Advances in Neurology, edited by M. Critchley et al. New York: Raven Press, 1982.

8. Kirn, T. "Discussion, ideas abound in migraine research; consensus remains elusive." JAMA 257(1):9-12, 1987.

9. Gelmers, H.J. "Calcium-channel blockers in the treatment of migraine." Am J Cardiol 55(3):139B-143B, 1985.

10. Blau, J.N. "Towards a definition of migraine headache." Lancet 1(8374):444-5, 1984.

11. Graham, J.R. "Migraine: questions, theories, and answers." Neurologic Clinics 1(2):551-66, 1983.

12. Fisher, C.M. "Late-life migraine accompaniments--further experience." Stroke 17(5):301-4,306, 1986.

13. Murray, J.B. "Psychophysiological aspects of migraine headaches." Psychol Rep 48(1):139-62, 1981.

14. Linet, M.S. and Stewart, W.F. "Migraine headache: epidemiologic perspectives." Epidemiol Rev 6:107-39, 1984.

15. Selby, G. and Lance, J.W. "Observations on 500 cases of migraine and allied vascular headache." J Neurol Neurosurg Psychiat 23:23-32, 1960.

16. MacDonald, J.T. "Childhood migraine. Differential diagnosis and treatment." Postgrad Med 80(5):301-4, 306, 1986.

17. Edelson, R.N. "Menstrual migraine and other hormonal aspects of migraine." Headache 25:376-9, 1985.

18. Bille, B. "Migraine in school children." Acta Paediatr. Scand 51(suppl. 136):3-151, 1962.

19. Waters, W.E. "Migraine: intelligence, social class, and familial prevalence." British Med J 2:77-81, 1971.

20. Waters, W.E. "Community studies of the prevalence of migraine." Headache 9:178-86, 1970.

21. Lucas, R.N. "Migraine in twins." J Psychosom Res 21:147-56, 1977.

22. Harvald, B. and Hauge, M. "A catamnestic investigation of Danish twins." Dan Med Bull 3:150-8, 1956.

23. Ziegler, D.K., Hassanein, R.S., Harris, D., and Stewart, R. "Headache in a non-clinic twin population." Headache 14:213-8, 1975.

24. Pearce, J.M. "Migraine: a cerebral disorder." Lancet 2(8394):86-9, 1984.

25. Liveing, E. Megrin, Sick Headache and Some Allied Disorders. London: Churchill, 1873. Cited in Kirn, T. "Discussion, ideas abound in migraine research, consensus remains elusive." JAMA 257(1):9-12, 1987.

26. Roy, C.S. and Sherrington, C.S. "On the regulation of the blood supply of the brain." J Physiol 11:85-108, 1890. Cited in Pearce, J.M. "Migraine: a cerebral disorder." Lancet 2(8394):86-9, 1984.

27. Sokoloff, L. "Local cerebral energy metabolism: its relationship to functional activity and blood flow." Ciba Fdn Symp no. 56 Amsterdam: Elsevier, 1978. Cited in Pearce, J.M. "Migraine: a cerebral disorder." Lancet 2(8394):86-9, 1984.

28. Lance, J.W., Lambert, G.A., Goadsby, P.J., and Duckworth, J.W. "Brainstem influences on the cephalic circulation: experimental data from cat and monkey of relevance to migraine." Headache 123:258-65, 1983.

29. Lauritzen, M. and Olesen, J. "Regional cerebral blood flow during migraine attacks by Xenon-133 inhalation and emission

tomography." Brain 107(Pt 2):447-61, 1984.

30. Olesen, J., Larsen, B., and Lauritzen, M. "Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine." Annals of Neurology 9:344-52, 1981.

31. Lauritzen, M., SkyhojOlsen, T., Lassen, N.A., and Paulson, O.B. "Changes in regional cerebral blood flow during the course of classical migraine attacks." Annals of Neurology 13:633-41, 1983.

32. Leao, A.A.P. "Spreading depression of activity in the cerebral cortex." J Neurophysiol 7:359-90, 1944.

33. Leao, A.A.P. "Pial circulation and spreading depression of activity in the cerebral cortex." J Neurophysiol 7:391-96, 1944.

34. Kraig, R.P. and Nicholson, C. "Extracellular ionic variations during spreading depression." Neuroscience 3:1045-59, 1978.

35. Moskowitz, M.A. "The neurobiology of vascular head pain." Annals of Neurology 16(2):157-68, 1984.

36. The Medical Letter on Drugs and Therapeutics. 29(735):27-8, 1987. New Rochelle: The Medical Letter, Inc.

37. American Hospital Formulary Service Drug Information 87. Edited by G.K. McEvoy. Bethesda: American Society of Hospital Pharmacists, 1987.

38. Kirn, T. "Migraine: many things to many patients." JAMA 257(1):12-3, 1987.

39. Nestvold, K. et al. Cephalalgia 5:115, 1985. Cited in The Medical Letter on Drugs and therapeutics. 29(735):27-8, 1987. New Rochelle: The Medical Letter, Inc.

40. Pradalier, A. et al. Cephalalgia 5:107, 1985. Cited in The Medical Letter on Drugs and Therapeutics. 29(735):27-8. 1987. New Rochelle: The Medical Letter, Inc.

41. Couch, J.R. and Hassanein, R.S. "Amitriptyline in migraine prophylaxis." Arch Neurol 36:695-9, 1979.

42. Powles, T.J. "Prevention of migrainous headaches by tamoxifen."(letter) Lancet 2(8519):1344, 1986.

43. Vincent, F.M. "Migraine responsive to danazol."(letter) Neurology 35(4):618. 1985.

44. Digre, K. and Damasio, H. "Menstrual migraine: differential diagnosis, evaluation, and treatment." Clin Obstet Gynecol 30(2):417-30, 1987.

45. Sargent, J., Solbach, P., Coyne, L., Spohn H. and Segerson, J. "Results of a controlled, experimental, outcome study of nondrug treatments for the control of migraine headaches." J Behavioral Med 9(3):291-323, 1986.

46. Levor, R.M., Cohen, M.J., Naliboff, B.D., McArthur, D. and Heuser, G. "Psychosocial precursors and correlates of migraine headache." J Consult Clin Psychol 54(3):347-53, 1986.

47. Harvey, P.G. and Hay, K.M. "Mood and migraine--a preliminary prospective study." Headache 24(2):225-8, 1984.

48. Schmidt, F.N., Carney, P., and Fitzsimmons, G. "An empirical assessment of the migraine personality type." J Psychosom Res 30(2):189-97, 1986.

49. Wolff, H.G. "Personality features and reactions for subjects with migraine." Arch Neurol Psychiat 37:895-921, 1937.

50. Alvarez, W.C. "The migrainous personality and constitution." Am J Med Sci 213:1-8, 1947.

51. Touraine, G.A. and Draper, G. "The migrainous patient." J Nerv Ment Dis 80:1-23, 183-204, 1934.

52. Furmanski, A.R. "Dynamic concepts of migraine." Arch Neurol Psychiat 67:23-31, 1952.

53. Mitchell K.R. and Mitchell, D.M. "Migraine: an exploratory treatment application of programmed behavior therapy techniques." J. Psychosom Res 15:137-57, 1971.

54. Kolb, L.C. "Psychiatric aspects of the treatment of headache." Neurology 13:34-37, 1963.

55. Friedman, A.P., and Merritt, H.H. Headache: Diagnosis and Treatment. Philadelphia: F.A. Davis Co., 1957. Cited in Linet, M.S. and Stewart, W.F. "Migraine headache: epidemiologic perspectives." Epidemiol Rev 6:107-39, 1984.

56. Sacks, O. Migraine: The Evolution of a Common Disorder. London: Faber and Faber, 1971. Cited in Schmidt, F.N., Carney, P, and Fitzsimmons, G. "An empirical assessment of the migraine personality type." J Psychosom Res 30(2):189-97, 1986.

57. Bille, B. The prognosis of migraine in children." Dan Med Bull 22:112, 1975.

58. Bildhorff, J.P., King, S.H., and Parnes, L.R. "Psychological factors in headache." Headache 11:117-27, 1971.

59. Maxwell, H. Migraine. Bristol: John Wright, 1965. Cited in Linet, M.S. and Stewart, W.F. "Migraine headache: epidemiologic perspectives." Epidemiol Rev 6:107-39, 1984.

60. Davis, R.A., Wetsel, R.D., Kashiwagi, T., and McClure, J.N. "Personality, depression, and headache type." Headache 16:246-51, 1976.

61. Henryk-Gutt, R. and Rees, W.L. "Psychological aspects of migraine." J Psychosom Res 17:141-53, 1973.

62. Kashiwagi, T., McClure, J.N. and Wetzel, R.D. "Headache and psychiatric disorders." Dis Nerv Sys 33(10):659-663, 1972.

63. Kudrow, L. "Current aspects of migraine headache." Psychosom 19:48-57, 1978.

64. Cassidy, W.L., Flanagan N.B. and Spellman, M.E. "Clinical observations in manic-depressive disease." JAMA 164:1535-46, 1957.

65. Diamond, J. "Depressive headaches." Headache 4:255-8, 1964.

66. Garvey, M.J., Tollefson, G.D., and Schaffer, C.B. "Migraine headaches and depression." Am J Psychiatry 141:986-8, 1984.

67. Crisp, A.H., Kalucy, R.S., McGuinness, B., Ralph, P.C. and Harris, G. "Some clinical, social and psychological characteristics of migraine subjects in the general population." Postgrad Med 53:691-7, 1977.

68. Pauline, J.M., Waal-Manning, H.J., Simpson, F.O. and Knight, R.G. "The prevalence of headache in a small New Zealand town." Headache 25:147-51, 1985.

69. Merikangas, K.R., Risch, N.J., Merikangas, J.R., Weissman, M.M. and Kidd, K.K. "Migraine and depression: association and familial transmission." (In Press)

70. Danforth, D.N. and Scott, J.R., editors. Obstetrics and Gynecology Fifth Edition. Philadelphia: J.B. Lippincott, 1986.

71. Welch, K.M.A., Darnley, D. and Simkins, R.T. "The role of

estrogens in migraine: a review and hypothesis." Cephalalgia 4:227-36, 1984. Cited in Digre, K. and Damasio, H. "Menstrual migraine: differential diagnosis, evaluation, and treatment. Clin Obstet Gynecol 30(2):417-30, 1987.

72. Whitty, C.W. and Hockaday, J.M. "Migraine: a follow-up study of 92 patients." British Med J 1:735-6, 1968.

73. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Published by the American Psychiatric Association. Washington, D.C. 1987.

74. Frank, R.T. "The hormonal causes of premenstrual tension." Arch Neurol Psychiatry 26:1053-1057, 1931.

75. Rubinow, D.R. and Roy-Byrne, P.P. "Premenstrual syndromes: overview from a methodologic perspective." Am J Psychiatry 141:163-172, 1984.

76. Strickler, R.C. "Endocrine hypothesis for the etiology of premenstrual syndrome." Clin Obstet Gynecol 30(2):377-385, 1987.

77. Roy-Byrne, P.P., Hoban, M.C., and Rubinow, D.R. "The relationship of menstrually related mood disorders to psychiatric disorders." Clin Obstet Bynecol 30(2):386-395, 1987.

78. Halbreich, U. and Endicott, J. "The relationship of dysphoric premenstrual changes to depressive disorders." Acta Psychiatr Scand 71(4):331-8, 1985.

79. Spitzer, R.L., Endicott, J. and Robins, E. "Research diagnostic criteria: Rationale and reliability." Arch Gen Psychiatry 35:773-779, 1978.

80. Endicott, J. and Spitzer, R.L. "Use of the research diagnostic criteria and the schedule for affective disorders and schizophrenia." Am J Psychiatry 136:52-59, 1979.

81. Endicott, J. and Spitzer, R.L. "A diagnostic interview: The schedule for affective disorders and schizophrenia." Arch Gen Psychiatry 35:780-782, 1978.

82. Weissman, M.M., Merikangas, K.R. and Boyd, J.H. "Epidemiology of affective disorders." In: Helzer, J.E. and Guze, S.B. (eds) Psychosis, Affective Disorders, and Dementia, in Michels, R. (Chair, Ed.Bd.), Cavenar, J.O., Jr. (ed): Psychiatry, Vol. I. p. 1-14. Philadelphia: J.B. Lippincott, 1985.

83. Keye, W.R. "General evaluation of premenstrual symptoms." Clin Obstet Gynecol 30(2):396-407, 1987.

YALE MEDICAL LIBRARY
3 9002 01012 9642
YALE MEDICAL

YALE MEDICAL LIBRARY

Manuscript Theses

Unpublished theses submitted for the Master's and Doctor's degrees and deposited in the Yale Medical Library are to be used only with due regard to the rights of the authors. Bibliographical references may be noted, but passages must not be copied without permission of the authors, and without proper credit being given in subsequent written or published work.

This thesis by has been used by the following persons, whose signatures attest their acceptance of the above restrictions.

NAME AND ADDRESS	DATE